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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/520,791	01/08/2005	Alexander Domling	62660(52171)	3248

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EXAMINER	
GUDIBANDE, SATYANARAYAN R	
ART UNIT	**PAPER NUMBER**
1654	

DATE MAILED: 01/23/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/520,791	DOMLING ET AL.	
	Examiner	Art Unit	
	Satyanarayana R. Gudibande	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7-17* is/are pending in the application.

4a) Of the above claim(s) 11 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7-10 and 12-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/02/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election of species as compound recited in claim 14 and 17, and addition of claims 14-17 in the reply filed on December 2, 2005 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claim 11 withdrawn from consideration as not directed to the elected species.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 7-10 and 12-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sasse, et al., The Journal of Antibiotics, 2000, 53, 879-885, in view of Greenwald, Journal of Controlled Release, 2001, 74, 159-171.

In the instant case, applicants claim a compound of formula represented in claim 14, where 'V' is an oxygen atom and the compound is pegylated with a spacer or linker. Applicants also claim a method of treating cancer patients with one or more compounds of formula shown in claim 14.

Sasse, et al., teaches the Tubulysin compound claimed by the applicant where the 'V' is an oxygen atom. The reference does not teach the linker and the PEGylation of the molecule.

Polyethylene glycol (PEG) is a non-ionic polymer and requires further modification for it to be conjugated to other molecules of interest. Therefore, in order to couple the PEG to other molecules the PEG is activated via introducing a linker between the active moiety and PEG. When such an activated PEG is used in the formation of a conjugate, it is obvious to obtain a linker or spacer-arm between the molecule of interest and PEG. It is obvious to PEGylate a molecule for various beneficial reasons such as increased half-life, improved solubility, etc. Greenwald, teaches PEG-anticancer drug conjugates. The reference of Greenwald teaches that conjugates of drugs with higher molecular weight PEG(>20,000d) improve the solubility and half-life of the drug in mouse model (abstract).

In the present instance applicants claim Tubulysin molecule conjugated to PEG molecule via a linker to facilitate in treatment of cancer in patients. Sasse, et al, discloses isolation and physico-chemical properties of tubulysin molecule. The reference of Sasse, et al., also teaches that tubulysin was soluble in methanol, acetone and ethyl acetate and hence the aqueous

solubility of the compound was quite low as disclosed in the reference (Physico-chemical properties, page 881). Greenwald teaches that PEGylation of compounds improves solubility of the compounds otherwise sparingly soluble in aqueous medium and increases the half-life of the compounds in vivo.

It would have been obvious to one of ordinary skill in the art at the time of the invention to have PEGylated the tubulysin, because PEGylation has been shown to increase the biological half-life and at the same time retain the biological activity of the peptides to which they are attached to as taught by Greenwald.

One would have been motivated to make the PEGylated tubulysin for the benefit of increasing the solubility of tubulysin in aqueous medium, increasing the half-life and clearance time, thereby reducing both toxicity, and improving the resistance to proteolysis, while retaining biological activity of the tubulysin.

One of ordinary skill in the art would have had a reasonable expectation for success in making the PEGylated tubulysin, as PEGylation of peptides is a routine technique widely practiced in the peptide arts for the reasons stated *supra*, as taught by Greenwald.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in making the PEGylated tubulysin. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 7-10 and 12-17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. In the instant case, applicants claim a numerous compounds represented by formula I of claim 7.

The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in Wands states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (Wands, 8 USPQ2sd 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (Wands, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

(1) The nature of the invention and (2) the breadth of the claims:

The claims are drawn to the numerous compounds represented by formula-I wherein the compound is pegylated via a linker. Thus, the claims taken together with the specification imply that all the compounds represented by formula-1 will have the desired anticancer activity.

(3) The state of the prior art and (4) the predictability or unpredictability of the art:

Sasse, et al., have looked at tubulysin A, B, D and E isolated from different microorganisms in growth inhibition studies of different mammalian cell lines. Although, they were highly effective in mammalian cell cultures, they found >10 fold differences in activity. The unpredictability of the art stems from the fact that the applicants claim myriads of compounds represented by formula-I. Not all of these compounds are isolated from natural sources such as microorganisms. Applicants have not provided any structure/function therefore one skilled in the art cannot predict which molecular structure will show activity. Also, cannot predict what molecular structures could be isolated from new strains of microorganisms. In the absence of a synthetic scheme to synthesize numerous compounds claimed by the applicants, the specification does not enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

(5) The amount of direction or guidance presented and (6) the presence or absence of working examples:

The specification has provided methods for making three variants of tubulysin A conjugated to PEG. However, the specification does not provide guidance either to isolate numerous compounds represented by formula-I from natural sources, or it provides guidance in the form of synthetic schemes as to how these compounds are made.

(7) The quantity of experimentation necessary:

One has to either develop synthetic methods to synthesize other compounds or isolate new compound from different strains of microorganisms and then do the testing for efficacy on a trial and error basis. This constitute tremendous burden on one skilled in the art to practice the invention.

It is the Examiner's position that one skilled in the art could not practice the invention commensurate in the scope of the claims without undue experimentation. It is also noted, considering the *a priori* unpredictability in the art with regard to isolation and/or synthesis of the numerous compounds represented by formula-I, that prevention and/or treatment of cancer using the numerous compounds is not enabled.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claim 7-10 and 12-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term 'biomolecule' has not been adequately defined in the specification. It is vague and indefinite as to what is a biomolecules?, and what is not a biomolecules.

Conclusion

Claims 7-10 and 12-17 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Satyanarayana R. Gudibande whose telephone number is 571-272-8146. The examiner can normally be reached on M-F 8-4.30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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